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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 3-(4-(4-(1H-BENZO[d] IMIDAZOLE 2-YL) PHENYLAMINO) THIAZOL-2-YL)-2-PHENYL THIAZOLIDIN-4-ONE DERIVATIVES

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ABSTRACT

As a part of systematic investigation of synthesis, characterization of 3-(4-(4-(1H- benzo[d] imidazole-2-yl)phenylamino)thiazol-2-yl)-2-phenylthiazolidin-4-one **(5)** compounds have been synthesized from N^4-(4-(1H-benzo [d] imidazol-2-yl) phenyl) thiazole-2,4-diamine **(3)** condensation-cyclization of aromatic aldehydes followed by thioacetic acid gives the desired compound **(5)**. All the synthesized compounds have been characterized by ^{1}H NMR; IR spectral data. These have been screened for their antifungal activity.

Key words: Benzimidazole, Thiazolidin-4-one, Antifungal activity.

INTRODUCTION

The class of heterocycles makes up important group of compounds due to their expansive range of applications[1] particularly N-heterocyclic compounds like, benzimidazole, thiazoles and it has been considered as one of the most important heterocyclic rings and very useful intermediates for the development of molecules of pharmaceutical or biological interest[2]. Various benzimidazole derivatives are well known to possess pharmacological and biological activities such as anti tumor[3], antimicrobial[4,5], antihelmenthic[6], anti cancer[7], antiinflamatory[8], analgesic[9] etc.

The literature revealed that the substitutions at the 1, 2 and 5 positions of the Benzimiazole moieties are exhibiting various pharmacological activities. Specifically, 2-substituted analogs of benzimidazole are known to be potent biodynamic compounds[10] are a large number of interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolo benzimidazoles), and two heteroatom (pyrazolo, imidazo, oxazolo, and thiazolo-benzimidazoles) and three heteroatoms (triazolo, thiadiazolo and

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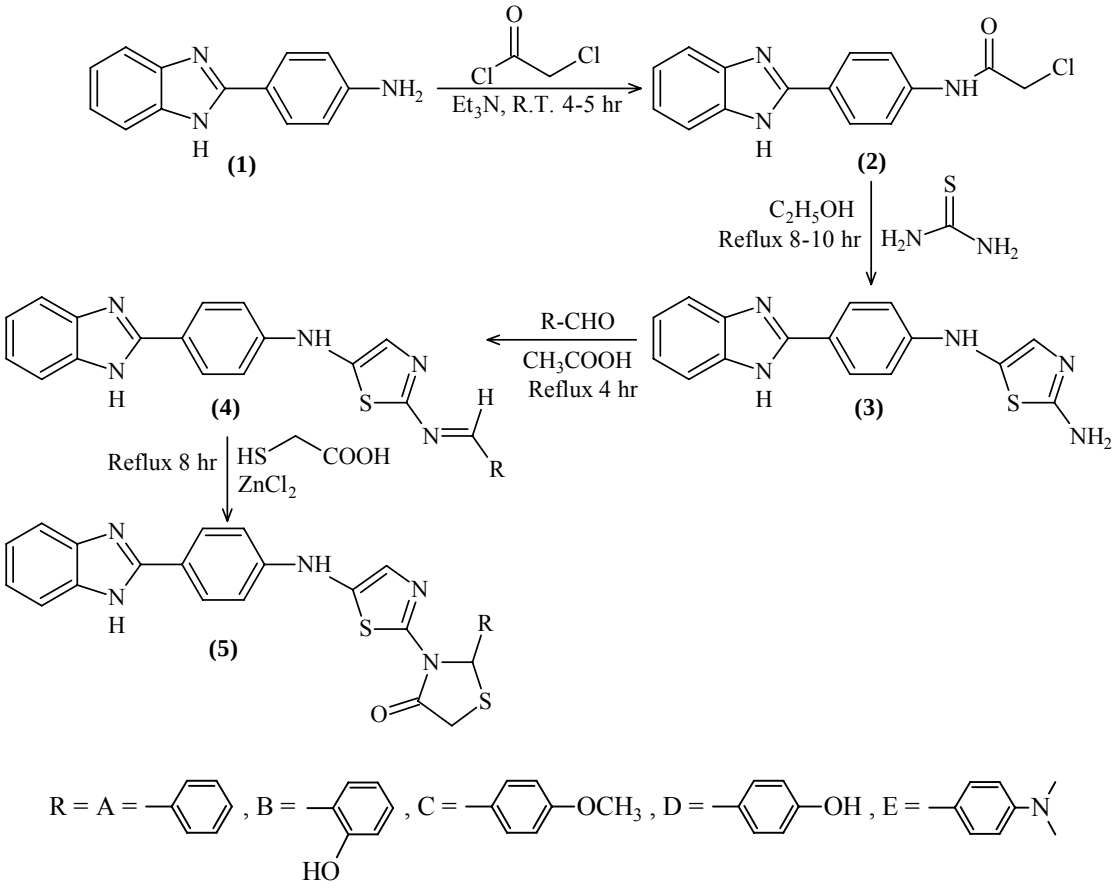
oxadiazolo benzimidazoles) and the derivatives of 4-thiazolidinone nucleus have occupied a unique place in the field of medicinal chemistry due to wide range of biological activities like antibacterial, antitubercular, anticancer, anticonvulsant and antifungal[11].

EXPERIMENTAL

Materials and methods

Melting points were determined in open capillary tubes and are uncorrected. Progress of the reaction was monitored by TLC plates, ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument in DMSO/$CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer; elemental analyses were performed on a Perkin-Elmer 240 CHN analyzer.



Scheme

Synthesis of 4-(1H-benzo[d]imidazol-2-yl) aniline (1)

A mixture of p-amino benzoic acid (0.03 mmol) and o-phenylenediamine (0.03 mmol) and $NaHSO_4$-SiO_2 (25% wt.) in 10 mL of ethanol was heated under reflux at 180ºC for 4 hr. The reaction mixture was partially cooled, poured on to crushed ice and neutralized with 10% NaOH solution. The precipitated product was collected by vacuum filtration, washed with excess 10% NaOH solution was dried and recrystallized from ethanol.

Synthesis of N-(4-(1H-benzo[d]imidazol-2-yl) phenyl)-2-chloroacetamide (2)

In an ice bath, a solution of compound 1 (10 mmol) and triethylamine (0.5 mL) in dry benzene (10 mL) was stirred for 15 min 10 mmol of chloroacetyl chloride was added and the reaction mixture was stirred for 4-5 hr. After completion of the reaction, the mixture was poured, with continuous stirring, on crushed ice. The solid formed was collected by vacuum filtration, washed with ethyl acetate, and recrystallized from ethanol.

Synthesis of N4-(4-(1H-benzo [d] imidazol-2-yl) phenyl) thiazole-2, 4-diamine (3)

To a solution of compound 2 (0.01 mol) in ethanol (150 mL), thiourea (0.01 mol) was added. This reaction mixture was heated under reflux for 8-10 hr with occasional stirring. Then, the reaction mixture was concentrated, and the residue obtained was poured over crushed ice and then crystallized from methanol and ethyl acetate. The base was liberated by dissolving the hydrochloride in water and basifying with a saturated solution of sodium carbonate and with the water to liberate the base completely, dried and recrystallized from absolute ethanol to give compound 3.

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m-H_2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl), 5.46 (s, CH thiazole), 4.0 (s, NH_2 amino thiazole) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH- aromatic); 2,922 (CH- aliphatic); 1,603 (C=N aromatic); 1,548 (C=C aromatic); 3,217 (NH_2- thiazole); MS: *m/z* (%), 142 (M^+, 100%); Analytical calcd. for $C_5H_6N_2OS$:C, 42.24; H, 4.25; Found C, 42.20; H, 4.21.

Synthesis of N4-(4-(1H-benzo[d]imidazole-2-yl) phenyl)N2-phenylidene thiazole-2,4-diamine (4)

The equimolar amount of the compound 3 (0.01 mol) and different aromatic aldehydes (0.01 mol) in methanol (50 mL) and a few drops of glacial acetic acid were added

and the reaction mixture was refluxed for 4 hr. The reaction mixture was cooled, poured into ice-cold water, and the separated solid was filtered, dried, and recrystallized from appropriate solvents to furnish compound.

4a. M.P 251 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl)), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 8.1 (s, 1H –CH aldehyde); 7.6 (m 2H, H2, H4 benzene); 7.3 (m, 2H, H3, H5 benzene); IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,548 (C = Caromatic); 1541 (C-N-C); 710 (m-C-S-C); MS: *m/z* (%), 396 (M^+, 100%); Analytical calcd. for C_{23} $H_{18}N_5S$; c, 69.69; H, 4.54; N, 17.67; Found C, 69.90; H, 4.50; N, 17.65%.

4b. M.P 265 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 10.13 (s, 1H –OH); 5.23 (s, 1H CH thiazole); 7.1 (m 2H, H2, H4 benzene); 6.8 (m, 2H, H3, H5 benzene); IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3563 (OH-phenol); 3,278 (aminophenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,548 (C=C aromatic); 1563 (C-N-C); 665 (-C-S-C); MS: *m/z* (%), 413 (M^+, 100%); Analytical calcd. For $C_{23}H_{18}N_5OS$; C,66.82; H, 4.60; N, 16.94; Found C, 66.75; H, 4.30; N, 16.85%.

4c. M.P 260 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 6.3 (s, 1H CH thiazole); 7.5 (m 2H, H2, H4 benzene); 6.8 (m, 2H, H3, H5 benzene); 3.75 (s, 3H –OCH_3) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,548 (C=C aromatic); 1563 (C-N-C); 665 (C-S-C); 665 (C-O-C); MS: *m/z* (%), 426 (M^+, 100%); Analytical calcd. For $C_{24}H_{20}N_5OS$; C, 67.60; H, 4.69; N, 16.43; Found C, 67.55; H, 4.66; N, 16.38%.

4d. M.P. 282 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 6.3 (s, 1H CH thiazole); 7.9 (m 2H, H1, H5 benzene); 8.2 (m, 2H, H2, H4 benzene); IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3547(OH-benzene) 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,548 (C=C aromatic); 1541

(C-N-C); 665 (-C-S-C); 681 (C-O-C); MS: *m/z* (%), 412 (M^+, 100%); Analyticalcalcd. For $C_{23}H_{18}N_5OS$; C, 66.99; H, 4.36; N, 16.99; Found C, 66.95; H, 4.30; N, 16.95.

4e. M.P. 257 ± 2ºC ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m-H2,H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 6.3 (s, 1H CH thiazole); 7.40 (m, 2H, H2, H4 benzene); 6.8 (m, 2H, H3, H5 benzene); 2.85 (s, 6H-$CH_{3)2}$) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,548 (C=C aromatic); 1563 (C-N-C); 665 (-C-S-C); 665 (C-O-C); MS: m/z (%), 426 (M^+, 100%); Analytical calcd. for $C_{24}H_{20}N_5OS$; C, 67.60; H, 4.69; N, 16.43; Found C, 67.63; H, 4.67; N, 16.40%.

Synthesis of 3-(4-(4-(1H-benzo[d]imidazole-2-yl) phenylamino) thiazol-2-yl)-2-phenyl thiazolidin-4-one (5)

To the separate solutions of compounds 4 (0.02 mol) in DMF (50 mL), thio acetic acid (0.02 mol) and anhydrous $ZnCl_2$ (0.02 mol) was added and the mixture heated at reflex for 8 hr. After completion of reaction, excess of solvent was distilled off, then cooled, and poured on to crushed ice. Solids thus separated out were Crystallized from appropriate solvent to furnish compounds **5(a-e)**.

5a. M.P. 308 ± 2ºC ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 5.46 (s, 1H CH thiazole); 7.14 (m 2H, H2, H6 benzene); 7.14 (m, 2H, H3,H5 benzene); 3.38, 3.28 (s, 2H-CH_2 thiazolidinone) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,566 (C=C aromatic); 1725 (C=O); 710 (-C-S-C); 665; MS: *m/z* (%), 436 (M^+, 100%); Analytical calcd. for $C_{25}H_{18}N_5OS$; C, 68.80; H, 4.12; N, 16.05; Found C, 68.76; H, 4.10; N, 16.01%.

5b. M.P. 315 ± 2ºC ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 5.46 (s, 1H CH thiazole); 10.13 (s-OH); 3.38 (s, 1H thiazolidine) 6.61-6.70 (m, 2H H3, H5 phenol) 6.89-6.91 (m, 2H, H5, H6 phenol); 3.38, (s, 2H–CH_2 thiazolidinone) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1,566 (C=C aromatic); 1725 (C=O); 3565 (-OH) 689 (-C-S-C); 1543 (C-N-C). MS: m/z (%), 452 (M^+, 100%); Analytical calcd. for $C_{25}H_{18}N_5O_2S$; C, 66.37; H, 3.98; N, 15.48; Found C, 66.32; H, 3.93; N, 15.44%.

5c. M.P. 312 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m-2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 5.46 (s, 1H CH thiazole); 6.95 (m 2H, H2, H6 anisole); 6.65 (m, 2H, H3, H5 anisole); 3.38, (s, 2H–CH_2 thiazolidinone) IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=N aromatic); 1084 (-OCH_3) 1,566 (C=C aromatic); 1084 1729 (C=O); 689 (-C-S-C); MS: *m/z* (%), 466 (M^+, 100%); Analytical calcd. For $C_{26}H_{20}N_5O_2S$; C, 66.95; H, 4.29; N, 15.02; Found C, 66.91; H, 4.25; N, 14.08%.

5d. M.P. 321 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 5.24 (s, 1H CH thiazole); 7.14 (m 2H, H2, H6 Phenol); 7.14 (m, 2H, H3, H5 phenol); 3.69 (s, 2H-CH_2 thiazolidinone) IR (KBr) ν_{max} (cm^1); 3,390 (NH, benzimidazole); 278 (aminophenyl); 3,043 (N Haromatic); 2,922 (CHaliphatic); 1,603 (C=N aromatic); 1,566 (C=C); 1,729 (C=O); 689 (-C-S-C); MS *m/z* (%), 452 (M+, 100%); Analytical calcd. for $C_{25}H_{18}N_5O_2S$; C, 66.37; H, 3.98; N, 15.48; Found C, 66.32; H, 3.95; N, 15.42%.

5e. M.P. 310 ± 2°C ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm 7.70 (m, 4H, H4, H7 benzimidazole), 7.40 (m, 2H, H3, H5 benzimidazole) 7.23 (m, 4H H5, H6 amino phenyl), 6.52 (m, H2, H6 amino phenyl), 5.0 (s, 1H, NH benzimidazole), 4.0 (s, NH, amino phenyl); 5.46 (s, 1H CH thiazole); 7.14 (m 2H, H2, H6 benzene); 7.14 (m, 2H, H3, H5 benzene); 3.66 (s, 2H-CH_2 thiazolidinone); 2.85 (s, 6H-N-$(CH_3)_2$, IR (KBr) ν_{max} (cm^{-1}); 3,390 (NH, benzimidazole); 3,278 (amino phenyl); 3,043 (NH-aromatic); 2,922 (CH-aliphatic); 1,603 (C=Naromatic); 1,566 (C=Caromatic); 1730 (C=O); 689 (CSC); MS: *m/z* (%), 458 (M^+, 100%); Analytical calcd. For $C_{27}H_{23}N_6OS$; C, 70.74.80; H, 5.02; N, 18.77; Found C, 70.76; H, 4.96; N, 18.75%.

Antifungal activity

The following fungal species are used to assess the antifungal activity of compounds. These were obtained from Fungal Culture Collection Laboratory, Department of Microbiology, Kakatiya University, Warangal, Andhra Pradesh.

Candida albicns KUCC 23

Aspergillus Niger KUCC 29

Media for fungal cultures

Sabourad's Dextrose Agar Medium (SDA)

Peptone	10.00 g
Dextrose	40.00 g
Agar	20.00 g
Distilled water	1000 mL
pH	6.8

Assay

The antifungal activity of synthesized compounds was determined by agar well diffusion method[12]. The culture plates inoculated with test organisms were allowed to solidify and punched with sterile cork borer (7.0 mm diameter) to make open wells. The open wells were filled with 0.05 mL or 50 μL of the test compounds. The test was carried out on SDA Plates and incubated at 30°C and 22°C, respectively for 72 hrs. The zones of inhibition were measured and recorded.

RESULTS AND DISCUSSION

Current investigation is devoted towards the research and development of highly efficient heterocyclic molecules with therapeutic potential. Efforts of our studies includes the synthesis of phenyl thiazolo benzimidazoles derivatives **(5)** synthesized by different substituent basing thiazolidinones. Scheme of the present study is an extension of previously reported[13]. Compounds **(3-5)** were synthesized according to the described procedure[14]. In this scheme 3rd and 4th step mechanism involves was by initial formation of an imine (amine attacks the aromatic aldehyde), which undergoes attack by sulpher nucleophile, followed by intermolecular cyclization on elimination of water to gives the corresponding thiazolidinones. All the synthesized compounds were characterized by elemental analysis, IR and ^{1}H NMR spectral data.

Antifungal assay

Antifungal activity of the synthesized compounds resulted significant activities of all the compounds tested. Activity was observed in dose dependent manner. Among the compounds screened derivatives of compound **5 (5a-5e)** showed highest inhibition zones among the tested organisms. Highest zone of inhibition 13 was noticed with compound **5e**

compared to other compounds. *Aspergillus niger* was the most susceptible species towards the compounds tested. On the other hand, *Candida albicans* also showed susceptibility for the compounds screened. However, derivatives of compound **4 (4a-4e)** showed lesser activity compared to the derivatives of compound **5**. The highest zone of inhibition showed by derivatives are compared with known standard nystatin at 10 mg/mL (Table 1).

Table 1: Anti-fungal activities of the derivatives of compound 4 and 5

Organisms	Compounds Zone of inhibition in mm										
	4					5					
	4a	**4b**	**4c**	**4d**	**4e**	**5a**	**5b**	**5c**	**5d**	**5e**	**Nystatin**
Aspergillus niger	5	7	3	5	8	8	10	8	7	13	19
Candida albicans	3	2	5	7	5	8	9	7	6	11	14

CONCLUSION

The present study reports successful synthesis of compounds **4 (a-e)** and **5 (a-e)** in good yield and these compounds exhibit moderate anti-fungal activity.

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